Intratumoral delivery of aluminum hydroxide-tethered IL-12 induces potent tumor-immune response

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Abstract

IL-12 is a potent cytokine that can mediate tumor immunity and tumor response. Its clinical development has been hindered by systemic toxicity. Intratumoral (IT) delivery can improve the therapeutic window of cytokine drugs by localizing treatments at the site of disease. In this study, we describe the development of a novel drug delivery platform for locally delivering cytokines that can be conjugated to aluminum hydroxide for systemic release. This platform is being used to develop a novel antitumor approach against human melanoma.

Figure 1: Schematic of anchored immunotherapy platform: Cytokines or other immune agonists of interest are genetically fused to a proprietary alum binding peptide (ABP) and co-delivered with Alhydrogel® (Alum). The co-delivered cytokine-Alum complex is then administered via intratumoral injection. The tumor immune responses are subsequently analyzed using Nanostring analysis.

Figure 2: Heat map showing changes in immune cell infiltration after treatment with either vehicle or the IT dose of 20 μg mANK-101. The RNA from tumor tissue harvested on Day 7 was analyzed using the nSolver analysis software with advanced analysis. (A) Heatmap representing changes in cell infiltration.

Figure 3: IL-12p70 activity in plasma (pg/mL) following treatment with vehicle or either dose of mANK-101. IL-12p70 activity was measured using a Bio-Plex Pro assay. (A) IL-12p70 activity following treatment with vehicle or either dose of mANK-101.

Figure 4: Enhanced Tumor Retention and Monotherapy Efficacy

Figure 5: mANK-101 Elicits Robust Immune Infiltration

Figure 6: mANK-101 Mediates both In innate and Adaptive Immunity

Figure 7: Combination with Checkpoint Blockade

Conclusions

- Ankyra's anchored immunotherapy platform forms an external delivery depot that improves the therapeutic window of cytokine and immune agonist drugs, and reduces the need for repeated injections.
- mANK-101, a stable complex of human IL-12 with its proprietary ALP, potently activates IL-12 in vivo.
- In vivo, mANK-101 stimulates robust innate and adaptive immune responses, without systemic toxicity and reduced body weight loss. Tumors are rechallenged with 5x10^6 B16F10 cells on Day 7 post-treatment.
- Antitumor activity was observed in both naive and B16F10-injected Balb/c mice.
- Tumor regressions were observed in both naive and B16F10-injected Balb/c mice.
- Tumor responses are associated with an increase in T cell infiltration, reduced inflammation, and reduced inflammation of immune cell and adaptive immune response.
- mANK-101 is a promising immunotherapeutic agent for the treatment of cancer.